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Toward developing models to study the disease, ecology, and evolution of the eye in Mollusca*

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Abstract: Several invertebrate systems have been developed to study various aspects of the eye and eye disease including *Drosophila*, *Planaria*, *Platynereis*, and most recently, the cubozoan jellyfish *Tripedalia*; however, molluscs, the second largest metazoan phylum, so far have been underrepresented in eye research. This is surprising as mollusc systems offer opportunities to study visual processes that may be altered by disease, vision physiology, development of the visual system, behavior, and evolution. Malacologists have labored for over a century as morphologists, systematists, physiologists, and ecologists in order to understand the structural and functional diversity in molluscs at all levels of biological organization. Yet, malacologists have had little opportunity to interact with researchers whose interests are restricted to the biology and development of eyes as model systems as they tend not to publish in the same journals or attend the same meetings. In an effort to highlight the advantages of molluscan eyes as a model system and encourage greater collaboration among researchers, I provide an overview of molluscan eye research from these two perspectives: eye researchers whose interests involve the development, physiology, and disease of the eye and malacologists who study the complete organism in its natural environment. I discuss the developmental and genetic information available for molluscan eyes and the need to place this work in an evolutionary perspective. Finally, I discuss how synergy between these two groups will advance eye research, broaden research in both fields, and aid in developing new molluscan models for eye research.

Key words: retina, photoreceptor, opsin, Pax6

Traditional model systems to study eyes

There is a great diversity of metazoans, but research on developmental processes has largely focused on a small number of "representative" species. The traditional "big six" model organisms used in developmental biology are the roundworm *Caenorhabditis elegans*, the fly *Drosophila melanogaster*, the zebrafish *Danio rerio*, the African clawed frog *Xenopus laevis*, the chicken *Gallus gallus*, and the mouse *Mus musculus*. These species were developed as model organisms because they are amenable to experimental and/or genetic manipulation and possess life history characteristics suitable for life in the laboratory, *i.e.*, they are easy to obtain, breed readily, and are fecund. Research focused on these six model animals has resulted in large-scale genome sequencing efforts, and complete or near complete inventories of genes and high-resolution genome maps are now available for all six species (Waterson *et al.* 2002).

Of the two traditional invertebrate models, *Caenorhabditis elegans* and *Drosophila melanogaster*, only *Drosophila* possesses eyes. The *Drosophila* compound eye has been an outstanding model system to study many general developmental processes including cell fate specification, cell division, growth, and death (Pappu and Mardon 2004). In addition to exploring cellular biology, researchers have determined the molecular basis of eye specification by genetically dissecting the fly eye to understand how it works. We have discovered how a group of multipotent cells (stem cells) can be converted to eye primordia during eye organogenesis and have identified the set of nuclear genes that regulate retinal specification. Understanding these genetic mechanisms involved in eye formation gives researchers crucial information on the origin of eye disease—which is when the genetic program goes wrong.

The *Pax6* paradigm

Comparative work with the *Drosophila* eye and vertebrate eye indicates that all eyes may share a similar developmental pathway in eye formation (Fig. 1). This has been referred to as the *eyeless*/*Pax6* paradigm (Donner and Maas 2004), which states that a single homologous genetic network regulates eye formation, regardless of eye type, across all metazoans, and the *Pax6* gene or its homologs are part of this regulatory gene network (Fig. 1A). There are three lines of evidence for this conclusion. First, the gene *eyeless* (*ey*) in *Drosophila* is homologous to the genes *Small eye* of mice and *Aniridia* of humans (Quiring *et al.* 1994). These two verte-

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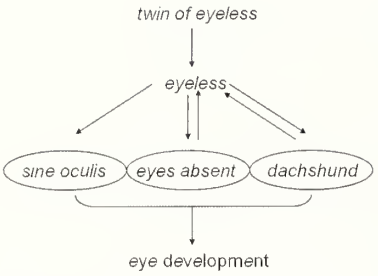
A



B

Drosophila	Vertebrate
eyeless / twin of eyeless	*Pax6* (9)
sine oculis	*Six* (6)
eyes absent	*Eya* (4)
dachshund	*Dach* (2)

Figure 1. A network of regulatory genes involved in eye formation conserved between *Drosophila* and vertebrates. A, The network of genes that regulates eye formation in *Drosophila*. Proteins from three genes in circles form biochemical complexes with each other in vertebrate models. B, List of vertebrate genes homologous to the *Drosophila* genes. Multiple vertebrate homologs, due to paralogous duplication, are indicated by numbers in parentheses (Relaix and Buckingham 1999, Donner and Maas 2004).

brate genes (*Small eye*, *Aniridia*) are collectively referred to as *Pax6*. This homology of *ey* and *Pax6* suggests that eye formation is controlled by a similar genetic mechanism in insects and vertebrates, despite large differences in eye morphology and development. Second, the *eyeless* gene has been shown to initiate eye formation. For example, when the *eyeless* gene in fly is mis-expressed (turned on in the wrong place at the wrong time, developmentally) eyes can be induced to form in wing, antennae, or leg primordia (Halder *et al.* 1995). Third, expression of *Pax6* gene copies from other species, including mice, squid, arrow-worm, and planaria, can also induce eye formation in *Drosophila* (Halder *et al.* 1995, Tomarev *et al.* 1997). The result of this work in *Drosophila* and vertebrates illustrates that there is a deep homology and conservation of eye genes in metazoans. This has lead some researchers (*e.g.*, Gehring and Ikeo 1999) to describe *Pax6* and its homologs as the "master control" gene for eye development in metazoans. We now know that this is an oversimplification of the system, and in fact, a number of other genes [*i.e.*, *eyes absent* (Bonini *et al.* 1997), *dachshund* (Shen and Mardon 1997), *sine oculis* (Pignoni *et al.* 1997) (Fig. 1B)] in addition to *Pax6*, are able to induce ectopic eye expression. Rather than a single gene, the *Pax6* paradigm really refers to a homologous genetic pathway that controls eye development across metazoans.

Molluscs as "non-traditional" model organisms for studying the eye

Despite the monumental advances in understanding eye development using traditional model organisms, it is important to include non-model systems in eye research. Broad comparative studies with many animal examples identify general evolutionary processes. Further, studying the eyes in multiple species expands our understanding of variation among eye types, how similar visual tasks many be performed under different conditions, how permutations at the structural level affect performance, and how gene and gene pathways evolve to create new phenotypes and subsequently, new functions.

In addition to the "traditional" *Drosophila* model, several other invertebrate organisms have been used to study the eye and eye disease including the flatworm *Planaria* (Saló and Baguñá 2002), the annelid *Platynereis* (Arendt *et al.* 2002), and most recently, the cubozoan jellyfish *Tripedalia* (Piatigorsky and Kozmik 2004, Nilsson *et al.* 2005). Work on planarian worms has provided a better understanding of eye formation, development, disease, and evolution of genetic networks (Pineda *et al.* 2000, Cebria *et al.* 2002), while *Platynereis* and *Tripedalia* have been used primarily as evolutionary models. *Platynereis* and *Tripedalia* models have broadened the evolutionary perspective of how eyes have evolved and what the ancestral eye condition may have been for Urbilateria (Arendt and Wittbrodt 2001, Arendt 2003, Piatigorsky 2003). Ultimately, these "non-traditional" models have given evolutionary depth to eye research by expanding work from the traditional model organism.

However, the second largest metazoan phylum, the Mollusca, has been underrepresented in eye research during the molecular age (post-*Pax6* paradigm) and has been underutilized in the study of developmental processes of the eye. This is surprising, as molluscan systems have shown potential for study of basic visual processes, physiology of vision, development of the visual system, and evolution. For example, past work (Robles *et al.* 1995, Torres *et al.* 1997) has shown that cytoskeletal organization of photoreceptor cells is regulated by the state of light- and dark- adaptation in cephalopod eyes. It is known that some disease states in the human retina, such as macular degeneration, affect cytoskeletal development and organization (Eckmiller 2004). Therefore, studies on cephalopod photoreceptors could lead to a better understanding of the role of the cytoskeleton in photoreceptor function and provide clues that link its organization to retinal disease. The goals of this paper are to: (1) provide an overview of the advantages of working with molluscan eyes; (2) describe the eye types found in molluscs; and (3) discuss the future directions of the field of eye research using molluscan models.

What is an "eye"?

An eye is a structure that can measure the amount of light (intensity) and compare light intensity from multiple directions (Land and Nilsson 2002). Therefore, eyes supply information of light distribution in the environment. Essentially, vision uses the principles of geometry to focus light

(optics) and chemistry to transform light energy into chemical signals. A nerve center, such as the brain or cerebral ganglia, then interprets these signals. Therefore, the ability of an organism to 'see', referred to as spatial vision, is the interpretation of the origin and direction of light, intensity, and contrast in the organism's environment. These attributes of light are the basis of pictorial information as resolved images.

The simplest way to produce spatial vision is to have series of light sensitive cells (photoreceptors) shielded on one side by dark pigment cells (Fig. 2). Pigment cells are often arranged in a cup-shape, which prevents all of the photoreceptor cells from detecting light from the exact same angular direction at the exact same time. Adding more photoreceptor cells and increasing the depth of the cup-shaped eye (Fig. 3A) increases sensitivity to the direction of light and refines the image (Land and Nilsson 2002).

In metazoans, there are two major types of photoreceptor cells, which use two different means of increasing the cell's surface area to better capture light (Table 1). Ciliary photoreceptors have an expansion of the ciliary membrane, while rhabdomeric (or microvillar) photoreceptors have an array of villi (microvilli) on the cell membrane (Eakin 1979). Each photoreceptor type is associated with specific families of photo-pigment molecules, such as opsin (r-opsin in rhabdomeric vs. c-opsin in ciliary cells), and proteins of the photo-transduction cascade which convert light energy into a membrane potential, an electrochemical signal (Arendt 2003, Nilsson 2004) (Table 1). Photoreceptors can either be excited by light and transmit information on light intensity and direction, or light may inhibit photoreceptor response so that neurons are activated only when light is terminated—resulting in a response to shadow (Land 1968). The eye can be specialized further with the addition of lenses (lenticular eyes; Fig. 3B) and corneas. These structures are found in some eyes to help focus light and the image onto the aligned photoreceptors that make up the retina.

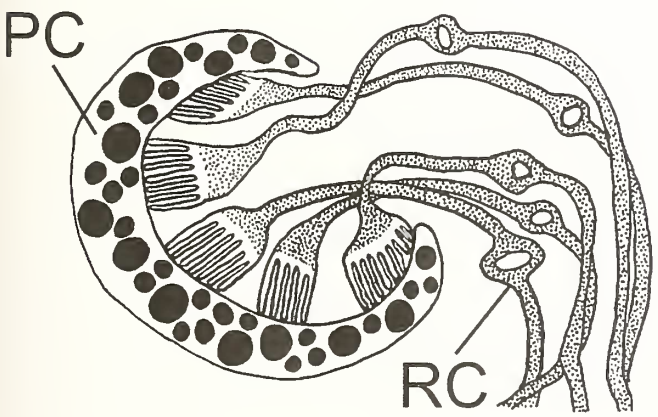


Figure 2. The simplest eye that produces spatial vision. Pigment cells (PC) are arranged in a cup-shape, which prevents all of the photoreceptor cells (RC) from detecting light from the exact same angular direction at the exact same time. Redrawn from Land and Nilsson (2006).

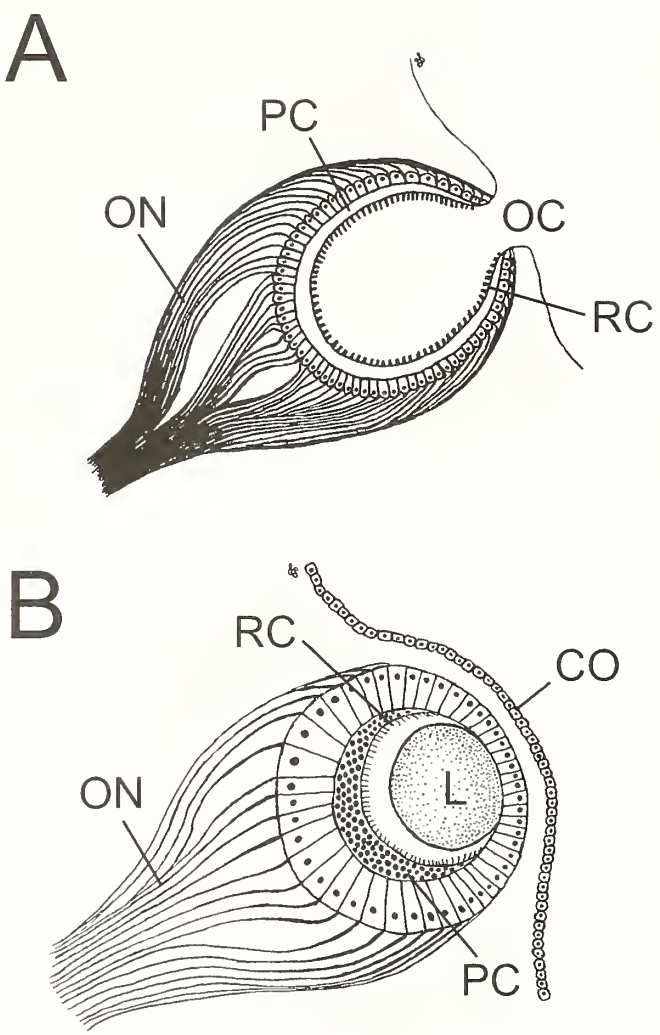


Figure 3. Two common eye types in molluscs. A, Open pit eye does not have a lens or cornea and is open to the environment (opening to optical cup; OC). B, Closed lenticular (lens) eye has both lens (L) and cornea (CO). Both eyes have optic nerves (ON), photoreceptor cells (RC), and pigment cells (PC).

Eye performance varies greatly among organisms and the specific eye structure that they possess. Performance of the eye can by summarized by two components: resolution and sensitivity (Land 1981, see Land and Nilsson 2002 for expanded explanation). Resolution is the precision with

Table 1. Characteristics of two photoreceptor cell types, rhabdomeric and ciliary. Information from Arendt (2003) and Nilsson (2004).

Photoreceptor cell type	Rhabdomeric	Ciliary
Membrane expansion	Microvillar	Ciliary
Photopigment molecule	Gq (G-protein)	Gi or Go[a] (G-protein)
Analogous proteins of phototransduction cascade	PLC (phospholipase enzyme)	PDE (phosphodiesterase)
	Arrestin-β	Arrestin-α
	rk 2, 3 (rhodopsin kinase)	rk 1 (rhodopsin kinase)
Membrane potential	Depolarizing	Hyperpolarizing

[a] Kojima *et al.* (1997).

which the eye can separate light according to its direction of origin and is directly related to the eye's ability to discriminate fine detail. Resolution depends on the number and spacing of photoreceptor cells in the retina. Sensitivity is the ability of the eye to capture enough light for photoreceptors to produce a usable neural signal, thus fully utilizing the potential resolution. Sensitivity can be increased by enlarging the aperture of the optical system, such as increasing the size of the pupil, or increasing photoreceptor diameter. However, increasing photoreceptor diameter decreases the number of photoreceptors in the retina, subsequently reducing the resolution of the eye. In general, a larger eye, with more photoreceptors and a large aperture, has both better resolution and sensitivity.

In molluscs, the placement of eyes is highly variable and may depend on both the function and the development of particular regions. In lineages such as gastropods and cephalopods, a pair of eyes is located on a well-developed head region; these are referred to as cephalic eyes. Other lineages with reduced head regions, such as polyplacophorans and bivalves, have many non-cephalic eyes. Some polyplacophoran species have eyes on exposed dorsal regions, while some lineages of bivalves have eyes on mantle tissue near siphons or along the valves.

The molluscan eye has many functions. Eyes are used for visually orienting the animal in its environment. For example, both bivalves and gastropods use visual cues: in bivalves, *Argopecten irradians* (Lamarck, 1819) appears to orient swimming behavior based on visual information (Hamilton and Koch 1996) while *Littorina* (Linnaeus, 1758) uses visual cues to discriminate between environments or objects (Evans 1961, Hamilton and Winter 1982). Eyes are also used to detect visual motion. For example, behavioral experiments in ark clams (Arcidae) *Arca noae* (Linnaeus, 1758) (Patten 1886), *Arca zebra* (Swainson, 1833), *Barbatia cancellaria* (Lamarck, 1819), and *Anadara notabilis* (Roding, 1798) (Nilsson 1994) suggest that the great number of eyes found on these species are used to detect motion, rather than responding to shadows. Ability to form an image also varies among molluscs. Coleoid cephalopods are probably best known for their excellent perception of images and ability to visual discriminate (review in Messenger 1981); perhaps lesser known is the wide degree of visual capabilities found among gastropods (Messenger 1981, Zieger and Meyer-Rochow 2008). Finally, it should be noted that mollusc eyes may also be important for migratory behaviors in pelagic and benthic species (Hamilton 1985).

Advantages and limitations to studying the molluscan eye

There are many advantages to working with a molluscan model to study the eye. First, molluscs provide an evolutionary perspective in eye research with a diversity of eye phenotypes within a single lineage rather than a comparison between the traditional model organisms that belong to disparate animal phyla. Although the *Drosophila* and vertebrate models have demonstrated the deep homology in eye genetics, we still lack a detailed understanding of what changes occur in these genetic networks that create the vast variation in morphology. With closely related mollusc lineages that possess different eye morphologies, we can tease apart changes at the gene level that alter phenotypes. Second, molluscs possess an array of visual adaptations found within a single species (*e.g.*, Groeger *et al.* 2006) or among closely-related species (*e.g.*, Kano and Kase 2002). These adaptations can be experimentally treated as "mutant" phenotypes, demonstrating the vast array of possible morphologies and providing a study system to examine specific genotypes that relate to phenotype. Third, molluscs are a powerful example of multiple, independently derived, image-forming eyes found across three (possibly four) classes. Multiple origins of complex structures allow researchers to test questions of gene or genetic network recruitment, an important mechanism that appears to have wide application to alter developmental processes resulting in novel phenotypes. Fourth, in molluscs a variety of eye types are expressed at different life stages within a single individual. This system can be used to test hypotheses of how duplication of orthologous or paralogous eye structures may have played a role in morphological and functional diversification of animal eyes (Oakley 2003, Friedrich 2006). Fifth, molluscs have the ability to regenerate their eyes, a reactivation of developmental processes in an adult organism to restore missing tissues (Butcher 1930,

Bever and Borgens 1988, Bobkova *et al.* 2004b). Regeneration occurs across many different animal lineages, including amphibians, molluscs, crustaceans, planaria, and cnidarians. Comparative studies to understand how vastly different organisms are able to regenerate organs will identify both differences and similarities in the genetic process, mechanisms, and elements, such as multipotent progenitor cells or pluripotent "stem cells." By determining the genetic mechanisms of regeneration across metazoans, we may be able to apply components of these processes to human medicine. Molluscs offer a unique system to study how optic nerves are repaired during regeneration, and may be a useful model to develop regeneration therapies. Finally, the large camera-like eyes of the coleoid cephalopods are morphologically and physiologically similar to a vertebrate eye, but offer unique research advantages and opportunities to study eyes without the disadvantages or constraints of working with a vertebrate system.

Despite these advantages to using the molluscan eye to study eye development and evolution, there are some limitations to our current knowledge of molluscan eyes. First, most information of eyes in molluscs comes from only a handful of species (Hamilton 1991). Second, there have been few comparative studies within lineages or within species (but see Bobkova *et al.* 2004a, Gál *et al.* 2004, Speiser and Johnsen 2008a), so we may be underestimating the degree of variation in eye structure and function. Since visual systems may change during the life time of an organism, due to metamorphosis or changes in environment/habitat (Groeger *et al.* 2005, 2006), additional work is needed to understand these fine and coarse modifications. Third, although we have identified eye or eye-like structures in many mollusc lineages, we know little about the function of these structures (see discussion on sensory structures of the Polyplacophora below) and how these structures may be important to the life cycle or ecology of the organism.

Types of molluscan eyes

The number of eye types in the Mollusca mirrors the incredible diversity in body plans in the phylum. Of the seven mollusc lineages, four (Polyplacophora, Bivalvia, Gastropoda, Cephalopoda) contain species with eyes that minimally consist of photoreceptors (arranged as a retina), pigment cells, and a lens. These four lineages represent the greatest biological diversity within the Mollusca, encompassing over 98% of recognized mollusc species (Ruppert and Barnes 1994). Below is a brief overview of the eye types found in these four molluscan classes. I chose to focus on only a few examples in each lineage and refer the reader to many excellent reviews where appropriate.

Polyplacophora

While most studies on the optics and fine-structure of the molluscan eye focus on the bivalves, gastropods, and cephalopods, the polyplacophorans have a unique system of photoreceptors and eye-like structures. There are no cephalic eyes in polyplacophoran species. Instead, chitons have developed three types of photoreceptors in the shell, a condition unique to Mollusca. Shell eyes, or aesthetes, are imbedded in the tegmentum that covers the shell plates (Blumrich 1891). Aesthetes are found in all chitons and may function as simple photoreceptors to meditate light-response behavior (Boyle 1977, see Knorre 1925 for alternative functions), and most likely do not provide visual information. Extra-pigmentary ocelli (Moseley 1885, Nowikoff 1907) and intrapigmentary ocelli (Nowikoff 1909) are restricted to few lineages in the family Chitonidae (Boyle 1977) and are believed to be photoreceptors capable of determining direction and intensity of light. Unlike the aesthetes, both ocelli types have lenses, a vitreous area, and a cup of retinal cells with microvillous rhabdomes (Boyle 1969b), the components necessary for spatial vision. Like other non-cephalic eyes in molluscs, the ocelli are highly repetitive structures, where a single individual of *Onithochiton neglectus* (Rochebrune, 1881) can have 411 to 1,472 ocelli in rows along all shell valves (Boyle 1969b). A detailed account of the orientation, patterning, and cellular structure of the externally pigmented eye is provided by Boyle (1969a, 1977). Reviews on chiton sensory organs can be found in Charles (1966), Boyle (1977), Messenger (1981), Kaas and van Belle (1985), and Serb and Eernisse (2008).

There is much work to be done to understand the function and ability of the different types of sensory organs in chitons. Optics, physiology, and function of the three sensory organs have not been examined in any detail. Thus, it is not known if the two ocelli types function as "eyes" with the capability of spatial vision. Further, there has been no recent work on visually mediated behavior. Until we have this basic knowledge of ocelli in chitons, polyplacophorans cannot used as effective models.

Bivalvia

There is an incredible amount of morphological variation in eyes of the Bivalvia (review in Morton 2001). Most bivalve eyes are not cephalic as bivalves do not have a distinct head. Instead, the majority of eyes in adults are found along the edge of the mantle, referred to as pallial eyes. This position of the eye appears to be a type of ectopic expression, and many species that possess pallial eyes have a large number of serially repeated eye structures along the mantle.

Two of the most complex and unusual eye types in bivalves are found in the ark clams (Arcoida) and the scallops (Pectinidae). The first description of eyes in ark clams

was Will (1844). Subsequent work by Patten (1886) and Nilsson (1994) refined the description of eye structure and examined eye function with visual behavioral experiments. Members of the Arcoida have two eye types: (1) a multifaceted compound eye which is similar in structure to the arthropod compound eye, but appears to be an independent origin of this eye type (Charles 1966, Nilsson and Kebler 2007) and (2) a simple pigment cup, or invaginate, eye (Fig. 3A). In contrast, Patten (1886, 1887) gives a description of three eye types: pseudo-lenticulate (groups of ommatidia, over which a cuticula is thickened to form a lens-like body), invaginate, and faceted (compound) eyes. However, recent treatments recognize only two eye types (Waller 1980, Nilsson 1994). Both eye types are found on the first outer mantle fold (Waller 1980), but the anterior-posterior patterning of the eyes varies across species and has been hypothesized to be related to the degree of light exposure of that portion of mantle edge (Waller 1980, Nilsson 1994). The eyes in Arcoida are highly repetitive structures, where a single individual may possess 200-300 compound eyes. This provides the animal overlapping visual coverage, which may improve sensitivity to the visual signal.

Based on measurements of eye performance calculated by eye anatomy, Nilsson (1994) suggests that the pallial eyes of ark clams function as optical "burglar alarms." According to this interpretation, these eyes are used to detect visual motion, rather than relying on a simple shadow response that can be accomplished by simple photoreceptors. The result is that the animal can respond to moving objects that do not cast a shadow. Although this means that ark clams have *spatial resolution* (ability to detect objects), it does not mean that they have the ability to visually reconstruct their environment, or *spatial vision* (Nilsson 1994). To date, the electrophysiology or neurophysiology of the ark clam eye has not been examined.

One of the best-known molluscan eye types is the mirror eye of the scallop (Pectinidae) and its close allies (Limidae, Spondylidae) (Patten 1886, Dakin 1910, 1928), where the image is not formed by the lens, but by reflection from the hemisphereical tapetum (argentea) that lines the back of the eye behind a double retina (description of optics in Land 1984). It has been demonstrated mathematically that the image forms on the distal retina, composed of ciliary photoreceptors (Land 1966a), and both physiological and behavioral experiments corroborate this finding (Patten 1886, Land 1966b). Pectinids respond to (1) an overall distribution of brightness in the environment, which determines the direction of swimming behavior via the proximal retina; local changes in (2) light intensity by shadow or (3) movements in the optical environment are involved in defensive responses via the distal retina (original description in Buddenbrock and Moller-Racke 1953, summary in Land 1968). So while the distal retina is used for focusing an image and detection of movement, the proximal retina response is to absolute levels of light intensity (Land 1966b). The two retinas function independently from one another with opposing responses to light (hyperpolarizing in distal retina vs. depolarizing in proximal retina) (Hartline 1938, Land 1966b, Gorman and McReynolds 1969, Gomez and Nasi 1994), are composed of different photoreceptor cell types (cilary vs. rhabdomeric) (Miller 1958), and use distinct phototransduction cascades (Kojima *et al.* 1997) (see Table 1).

Much work has been done on the scallop eye including recent work on optics (Land 1965, 1966a), comparative anatomy (Morton 2000, 2001 and references therein, Speiser and Johnsen 2008a), electrophysiology (Gorman and McReynolds 1969, Gomez and Nasi 1994), neurophysiology (Spagnola and Wilkens 1983, Wilkens 2006), visual-mediated behavior (Wilkens and Ache 1977, Hamilton and Koch 1996, Wilkens 2006, Speiser and Johnsen 2008b), phototransduction (Kojima *et al.* 1997), and lens formation and protein evolution (Carosa *et al.* 2002, Piatigorsky 2008).

The ark clam and scallop utilize two very different eye morphologies to obtain spatial information from their environments. Although the general structure of these eyes is not comparable, the functions may be quite similar. Yet, there has been much discussion of why a relatively sedentary organism, like a bivalve, would need such complex eyes and so many of them. Regardless of the specific function of bivalve pallial eyes, the large number found in scallops and ark clams strongly suggest that vision or visually mediated behaviors are extremely important to these species.

Gastropoda

Except for a few genera, most gastropods have a pair of cephalic eyes. Eye placement varies among gastropod groups, and the eye can be located at the base of cephalic tentacles, on the tips of retractable tentacles that can withdraw the eye, or on short stalks. Gastropod eyes range from open pits (Fig. 3A) to closed vesicles with or without lenses. The majority of gastropod eyes are of the closed lenticular type (Fig. 3B), composed of cornea, lens, vitreous body, and a cup-shaped retina (but see heteropods below). The retina can have multiple photoreceptor types (Table 1); however, the majority of photoreceptors near the lens are microvillous R cells that form rhabdomeres. Other photoreceptor cells (*e.g.*, H cells, basal retinal neurons -BRN) are ciliary (Chase 2002). Across species, there is considerable variation in retinal composition (number of cells, photoreceptor density, organization of photoreceptors) (Hamilton 1991, Chase 2002), but the functional significance of these differences largely is unknown and unexplored. Generally, gastropod eyes appear to have several functions including: mediating phototaxic behavior and locomotion, regulating daily and

seasonal activities, and, in some species, visual detection of forms. However, the extent to which gastropod eyes have spatial vision is still under investigation (Zieger and Meyer-Rochow 2008) and will probably vary greatly among species.

There are several unique structures in the gastropod sensory system. The "accessory retina" (Smith 1906) is found in some gastropod lineages (*e.g.*, Limacidae), which may be involved in infrared detection (Newell and Newell 1968). Dorsal eyes appear in species of the marine slug *Onchidium* Buchanan, 1800. These eyes are on papillae projecting off the dorsum of the animal (Hirasaka 1922) and are composed of ciliary photoreceptors that may create a "reasonable image" (Land 1968). See detailed descriptions in Katagiri *et al.* (2002) and references therein. Probably the most sophisticated and unique eye in the gastropods is the scanning lenticular eye of pelagic heteropods. The retina is not cup-shaped but forms a long strip of 3-6 cells in width, resulting in a very narrow field of view and contains several photoreceptor types that are unlike ciliary or rhabdomeric receptors found in cephalic eyes of other molluscs (Land 1984). These eyes move in a systematic scanning motion, which may be used to detect stationary objects (Land 1982). Further work on the function of these unusual eyes is needed. For more information on gastropod eye diversity, there are several excellent and comprehensive reviews (Charles 1966, Messenger 1981, Chase 2002, Zieger and Meyer-Rochow 2008).

Cephalopoda

Vision in cephalopods is quite different than the visual information available to most other molluscs as reflected by the sophisticated eye types found in this lineage. There are two well-known cephalopod eye types, the pin-hole eye type of nautiloids and the camera-type eye (Fig. 4) in coleoid (internal shelled) cephalopods. Eyes of *Nautilus* Linnaeus, 1758 are unusual as they are open to the environment, have no cornea or lens, and appear to function like a pin-hole camera (Messenger 1981). Although it would appear that this eye is rather unsophisticated, many other features suggest that the eye has an effective visual system. The *Nautilus* eye is large, comparable in size to the more elaborate camera-type of the coleoids, and has an adjustable pupil (Hurley *et al.* 1978). Having a large eye with a small aperture improves spatial resolution of the eye, until light capture is limited. In fact, calculations by Land (1981) suggest that the resolving power of a nearly closed pupil of *Nautilus* is on par with a typical insect eye. In the retina, density of closely packed rhabdomeric photoreceptors has been conservatively estimated at an order of magnitude higher than any other non-cephalopod mollusc (Barber and Wright 1969, Messenger 1981), again implying good capabilities for image resolution (but see Land 1981). In addition, the *Nautilus* eye

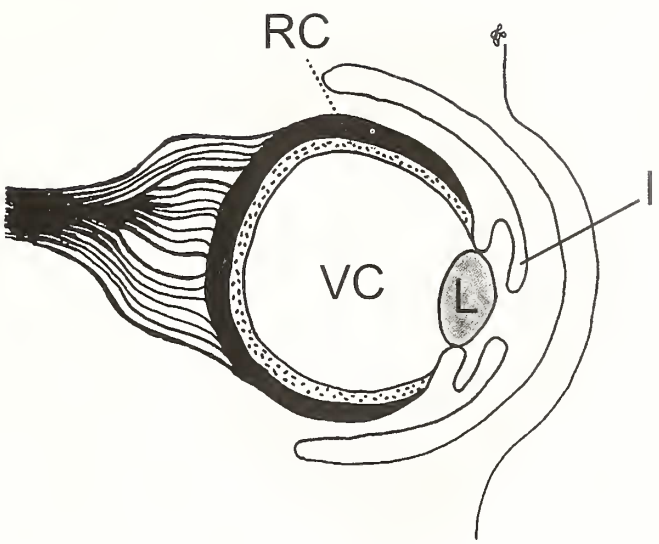


Figure 4. Camera-type eye of coleoid cephalopods has an iris (I), nearly circular lens (L), vitreous cavity (VC), and photoreceptor (RC) and pigment cells that form the retina. Redrawn from Zuker (1994).

possesses an ocular-motor reflex which compensates for movement of the animal and allows for the stabilization of images on the retina. This type of reflex is found only in animals that are able to detect motion and form, thereby suggesting *Nautilus* has these capabilities (Land 1981).

Although these eye properties are important in spatial vision, the function of the *Nautilus* eye is still speculative. It has been suggested that the *Nautilus* may use its eyes to stabilize itself under strong oceanic currents, help navigate during diurnal vertical migrations, or identify potential food sources (Muntz 1991); however, little is known of the *Nautilus* in its natural condition and these hypotheses remain untested. Many other questions about the fine structure of *Nautilus* eye also remain unanswered.

In contrast to the eye of the *Nautilus*, considerable information exists on the eye and visual capabilities of coleoid cephalopods due to detailed studies of optics, neurophysiology, retinal organization, and extensive behavioral experiments. Since these animals rely on vision for prey capture, predator avoidance, and intra-specific communication (Budelmann 1996, Hanlon and Messenger 1996, Muntz 1999), they possess excellent perception and visual acuity (Messenger 1981).

Coleolid cephalopods have rhabdomeric (microvillous) photoreceptors in a camera-type eye that optically functions in a similar manner to the vertebrate eye, making the cephalopod eye a famous example of convergent evolution (Packard 1972; however, see Serb and Eernisse (2008) and references within for alternative views). Specifically, the

cephalopod eye resembles an all-rod elasmobranch eye with similar optics, speed, sensitivity, and resolution (Packard 1972). Similarly, cephalopods have an iris, nearly circular lens, vitreous cavity, and photoreceptor cells that form the retina (Fig. 4); however, the photoreceptors in the cephalopod eye are rhabdomeric, not ciliary as in vertebrate eyes (Young 1962). Reviews on the similarities and differences of these eyes can be found in Packard (1972), Messenger (1981), Land (1984), Nicol (1989), Nilsson (1996), and Land and Nilsson (2002).

There is a large body of literature on the cephalopod retina. We have a good understanding of the retinal structure in both *Octopus* Cuvier, 1797 (for example, see early work in Babuchin 1864, Hensen 1865, summarized in Young 1962, Yamamoto *et al.* 1965, Messenger 1981) and squid (*Loligo* Lamarck, 1798) (Cohen 1973a, 1973b). Because the cephalopod retina is structurally simple, comprised of only a few cell types, it has been a favorite model system for the study of comparative physiology and photoreceptive mechanisms (Yamamoto *et al.* 1965). Other work on the cephalopod retina has focused on light/dark adaptation—how the eye acclimates to changes in light levels in the environment (Young 1963a). Work on cephalopods has identified important sub-cellular alternations to the shape of photoreceptor cells and movements of cytoskeleton and photopigments within these cells in response to changes in light intensity (Robles *et al.* 1995, Marinez *et al.* 2000, Gray *et al.* 2008). These studies have important application to understanding human eye disease. Another important question with medical applications is, how does the retina organize? While Meister (1972) provides a chronology of cell patterning and differentiation of the squid retina based on light microscopy, the next step is exploring the developmental regulation of the retina and how retinal cell fate is determined. This is a wide-open area for future research and will provide data to compliment work in mouse and other vertebrate models (Livesey and Cepko 2001, Zaghloul *et al.* 2005). These comparative studies of convergent structures will be an important contribution to both developmental and evolutionary biology.

Within coleolid cephalopods, there is both interspecific and intraspecific variation in their eyes. Some of these differences occur in the shape of the eye, which may deviate from spherical to telescopic (*Amphitretus* Hoyle, 1885), stalked (*Bathothauma* Chun, 1906), or asymmetrical (*Histioteuthis* Orbigny, 1841) eyes (Chun 1913, Nixon and Young 2003 and references therein). Composition of the eye may also vary. For example, the eyes of *Cirrothauma murrayi* (Eschricht, 1836) are simple open cups, lacking lens, iris, or ciliary body—the muscle and choroid surrounding the eye typically found in other coleolid cephalopods (Chun 1913). Patterning, size, and density of the rhabdoms in the retina vary among species (Young 1963b), and these traits appear to be correlated with the behavior and pupil shape (discussion in Messenger 1981). Absorbance and transparency of lenses can differ among species found a different depths (Denton 1960, Denton and Warren 1968, Sweeney *et al.* 2007b) as well as within a single species (Denton and Warren 1968). Finally, retinal sensitivity can vary during ontogeny. Recent work on the cuttlefish *Sepia officinalis* Linnaeus, 1758 indicates that aspects of the eye change during growth, including spectral sensitivity, light and contrast sensitivity, and visual acuity (Groeger *et al.* 2005, 2006).

The visual abilities in coleolid cephalopods have been explored more extensively than any other molluscan group (reviewed in Messenger 1981). Cephalopods display excellent perception and are able to discriminate between different shapes, but it appears that they are color blind (Messenger 1981, Mathger *et al.* 2006). So how do these cephalopods create and control their camouflage to imitate chromatically rich environments without color vision (Hanlon 2007)? An interesting solution has been suggested by Shashar and Cronin (1996). They propose that polarized vision may provide visual information to detect and recognize objects analogous to color vision systems. Polarized light sensitivity has been identified in many cephalopods (Moody and Parriss 1960, Jander *et al.* 1963, Tasaki and Karita 1966), suggesting its importance in the organism's ecology (*e.g.*, Waterman 1981), but the function of this sensitivity needs to be tested further.

FUTURE DIRECTIONS

Choosing a molluscan model

Considerations

To further advance eye research in molluscs, a directed and combined effort to develop one or several model species is needed. Some considerations in choosing a model organism should include its life history traits, the availability of the nuclear genome sequence of the target species or a closely related species, and a strong foundation of research in the eye system of that species (Bolker 1995, Slack 2006, Jenner and Wills 2007). For experimental work, it will be necessary to maintain the model organism for a period of time in the laboratory. Development and implementation of a new molluscan model species will depend on both species characteristics and laboratory considerations. For example, to maximize the number of possible laboratory experiments per year, it is optimal if both adults as well as embryos are available year-long by either culturing the species in the laboratory or collecting samples from wild populations. In addition, housing costs for the species must be considered,

especially if a colony needs to be maintained. Larger species will require more laboratory space, and marine species may be more challenging, especially if the species filter-feeds. For eye research, placement and size of the organ is also important. Eyes of potential model organisms must be easily accessible in the adult or at specific development stages, if experimental manipulation or explants are necessary. For questions concerning genetic processes, the model organism would need to be a laboratory-cultured species with quick embryonic development that reaches sexual maturity in a short period of time. In these cases, small animals would be preferred to house many individuals and to keep maintenance cost down. However, it has been pointed out that species selection based on rapid developmental rate and small body size may introduce bias such as developmental and genomic constraints or maternal influence (Bolker 1995, but see Jenner and Wills 2007 for the opposing view).

For nearly all eye research, an organism with a complete genome sequence would be advantageous. First, the availability of the complete nuclear sequence of a model organism gives the researcher a complete inventory of all genes in that organism. Second, identifying and isolating homologous genes in the new model organism becomes almost trivial compared to the laborious method of cloning homologous genes in a new species. Third, all members of a gene family could be identified in advance of the experiment. These data are essential to interpretation of gene function and its manipulation. Currently, Genbank of the National Center of Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/) lists three genome projects of mollusc species that are in progress or are being assembled and annotated. These include the freshwater snail *Biomphalaria glabrata* (Say, 1818) (Gastropoda: Basommatophora)—in progress (Washington University); the sea hare *Aplysia californica* Cooper, 1863 (Gastropoda: Opisthobranchia) (Broad Institute)—in assembly; and the marine clam *Spisula solidissima* Dillwyn, 1817 (Bivalvia: Veneroida) (Marine Biological Laboratory)—in progress. Another genome that is currently being annotated is the limpet *Lottia gigantea* Sowerby, 1834 (Gastropoda: Patellogastropoda) available at the Joint Genome Institute (JGI; http://genome.jgi-psf.org/Lotgi1/Lotgi1.home.html).

Finally, successful development of a molluscan model organism would benefit from a body of research already conducted on that species. Previous work on such topics as optics and visual behavior may direct the types of questions or direct which organism may be most appropriate for the project. That being said, development of a new model organism is a time consuming process as well as a large financial commitment for genomic resources and laboratory set-up. Only taxa that have multiple uses can realistically be considered.

Candidate model species

There are several molluscan species that meet several of the above criteria and make strong model organism candidates. *Aplysia californica* might be considered the highest priority for molluscan eye researchers. This species has been the "workhorse" for both physiology and neurobiology, and there is a large body of literature on the physiology, neurology (neurobiology, neural processes), photoreception, and visual-mediated behavior (Kandel 1979 and references therein). *Aplysia californica* has a pair of small (300-600 μm) cephalic eyes at the base of the posterior tentacles (rhinophores). The eye is a closed chamber with a large spheroid lens. The retina, which nearly surrounds the lens, appears to have both rhabdomeric and ciliary photoreceptors that interdigitate to form the rhabdomere (Jacklet *et al.* 1972). Based on the close proximity of lens to retina, the *A. californica* eye does not appear to have good spatial vision, but the eyes respond to light in three different ways (Jacklet 1969, 1973). This demonstrates that the two photoreceptor types respond differently to light, like the scallop, making this an interesting system. Keeping and culturing *Aplysia* in laboratory has been somewhat standardized (Kandel 1979), and the National Institute of Health (NIH) and University of Miami run a large-scale mariculture facility, the *Aplysia* Resource Facility, that can provide specimens from known genetic lines for researchers (http://www.rsmas.miami.edu/groups/sea-hares/), making availability of specimens a non-issue. In addition, the *Aplysia* genome has been sequenced and is being assembled.

A bivalve model for eye research might be a scallop species. There is a large body of literature on the scallop eye (see references above). Scallops are commercial species being cultured in aquaculture facilities for the global market, so it should be an easy transition to develop a facility for research. This also presents an opportunity to collaborate with aquaculture researchers to develop genomic tools and resources, such as sequencing the scallop genome.

Unlike *Aplysia* and scallops, cephalopods have large eyes making them easy to work with and manipulate. Several coleoid cephalopod species would make good model organisms to study the eye due to their availability. Three small species (*Sepia officinalis*, *Sepia pharaonis* Ehrenberg, 1831, and *Euprymna scolopes* Berry, 1913) are laboratory-cultured by the National Resource Center for Cephalopods (NRCC), which is funded by NIH's National Center for Research Resources and Texas Institute of Oceanography. As squids have been a popular model organism, many texts and protocols are available for eye and nervous system work (*e.g.*, Gilbert *et al.* 1990, Meinertzhagen 1990, Saibil 1990). Currently, an EST (expressed sequence tag) library for the eye is available for a related species, *Octopus vulgaris* Cuvier, 1797 (Ogura *et al.* 2004), which provides a list of genes expressed in a spe-

cific tissue (the eye) at a particular developmental stage (adult). This genomic resource could be applied to other cephalopod species as a list of candidate genes or as a starting point to isolate specific genes or gene families in cephalopod eyes. In addition, one of the transcription factors initiating eye organogenesis, the *Pax6* gene, has been isolated from the squid *E. scolopes* and there are developmental data on the role of *Pax6* in eye, brain, and sensory organ development (Tomarev *et al.* 1997). Detailed studies on the development of the eye and central nervous system in several species (Marthy 1973, Shigeno *et al.* 2001) and development and structure of the lens (West *et al.* 1995, Sweeney *et al.* 2007a) are available. A large body of literature exists for cephalopod ecology and how these organisms adapt to environmental conditions (Boyle and Rodhouse 2005 and references therein). Finally, cephalopods may be the best molluscan model for medical research because their eye structure and function are similar to the human eye.

Molluscan models in evolutionary biology

Molluscs are an excellent group for the study of evolutionary biology because, as a group, they possess a diverse set of eye phenotypes that range in complexity. For example, within a single lineage like Gastropoda, eye phenotypes range from simple pit eyes to complex lenticular eyes. Across Mollusca, nearly every eye type is represented as well as many unique phenotypes. Among metazoans, molluscan eyes will provide data for a more comprehensive view of eye evolution, rather than relying on a few model organisms found in widespread and distant phyla. In particular, molluscan eyes are a compelling case of multiple, independently derived, image-forming organs. Within the eye there are various levels of homology to examine, including the level of the gene and genetic network (*e.g.*, *Pax6* pathway), cell (*e.g.*, photoreceptor), or tissue type [lens protein evolution, (Carosa *et al.* 2002, Piatigorsky 2008)]. Below are some examples of evolutionary topics that can be addressed with molluscan eye models.

Testing the Pax6 *paradigm*

In a recent paper by Donner and Maas (2004), the genetic pathways used to create an eye were compared in *Drosophila* and vertebrates. The authors found that while all genes in the *Drosophila Pax6* pathway are expressed in the vertebrate eye during development, the functions and relationships of these homologous genes within their respective pathways have not been strictly conserved. This being the case, Donner and Maas (2004) argue that *Drosophila* is still a valuable study model and may be used to guide research on vertebrate eye development. They conclude (p. 750) that when the pathway is not strictly maintained between vertebrates and invertebrates, this indicates that "the particular role that the genetic [pathway] . . . is *either not relevant*, or *not sufficient, to meet the complexity of the vertebrate* [eye]" (my italics). One interpretation of these results is that conservation of genetic pathways between lineages will decrease as eye complexity increases, and eye types diverge, in one lineage. We can test this assertion in two ways using molluscan models. First would be to deal with a major shortcoming with the Donner and Maas' (2004) hypothesis, namely that their comparison was between two completely different eye types: the compound eye of *Drosophila* and the camera-type eye in vertebrates. A more appropriate test might be a comparison of two camera-type eyes—in cephalopods and in vertebrates—that are similar in function but vary in their degree of retinal complexity. Second, the hypothesis could further be tested by examining changes in the *Pax6* pathways and the resulting phenotype of the eye within a single molluscan lineage, such as gastropods or bivalves, that have multiple eye types ranging from simple photoreceptor eyespots to more complex lenticular eyes.

Using the molluscan eyes to examine evolution

The eye has long been a target of anti-evolutionists as an example of "irreducible complexity" (Behe 1996) The idea is that certain biological systems, such as eyes, are too complex to have evolved from simpler, less complete, prototypes and that these structures are too complex to have arisen from chance mutations (Hall and Hall 1975, Johnson 1991, Oakland and Matrisciana 1991, Behe 1996). Anti-evolutionists often cite a single sentence from Darwin's *Origin of Species* to demonstrate his own doubt in the ability of evolutionary forces to create the eye:

> "To suppose that the eye [in all of its complexity] . . . could have been formed by natural selection, seems, I freely confess, absurd in the highest possible degree" (Darwin 1859: 186).

Less often is Darwin's (1859: 186) next sentence cited, which states:

> "Yet reason tells me, that if *numerous gradations* from a perfect and complex eye to one very imperfect and simple, each grade being useful to its possessor, *can be shown to exist*; if further, the eye does vary ever so slightly, and the variations be inherited, which is certainly the case; and if any variation or modification in the organ be ever useful to an animal under changing conditions of life, then the difficulty of believing that a perfect and complex eye could be formed by natural selection, though insuperable by our imagination, can hardly be considered real" (my italics).

Molluscs, with their diversity of eye types, offer examples of

an "intermediate" eye types and the group is often cited as a counter-argument to anti-evolutionists. The range of eyes include the eye spot, pigment cup (Fig. 3A), pin hole camera eye (*Nautilus*), lenticular eye (*i.e.*, *Strombus* Linné, 1758; Fig. 3B), and the camera eye (*Octopus*; Fig. 4). However, it has not been demonstrated that a single lineage contains a plausible series of intermediate eye-designs to examine the gradient hypothesis. Gastropods may be a good group to test the gradient hypothesis as there are several lineages within the gastropods that contain variation in eye complexity. Once a species phylogeny has been constructed and eye types characterized on the tree, ancestral states of eye complexity can be estimated. In addition, the time to transition from one eye structure to another could be calculated. This would be an excellent test of Nilsson and Pelger's (1994) estimated time (about 0.5 million years) needed to evolve a lenticular eye from a simple photoreceptor patch.

Photoreceptor evolution

Both rhabdomeric and ciliary photoreceptors are found in two (*Aplysia* and *Pecten*) of three of potential molluscan model organisms, which is useful for testing current views of photoreceptor evolution. In a recent paper by Plachetzki *et al.* (2005), the authors argue for a common origin and subsequent divergence of photoreceptor cells in an early metazoan ancestor based on two lines of evidence. First, both rhabdomeric and ciliary photoreceptors have been found to coexist in many lineages, including vertebrates (Panda *et al.* 2005) and annelids (Arendt *et al.* 2004). These data are part of a growing body of evidence that is in contrast to previous hypotheses, where rhabdomeric photoreceptors are found mostly in invertebrates and ciliary photoreceptors generally occur in vertebrates (Eakin 1979, 1982; however, see Vanfleteren 1982 for a differing view). Second, rhabdomeric and ciliary photoreceptors can be identified by specific genetic signatures, which are gene expression specific to that particular cell type, such as opsin, *rx*, and atonal genes. However, molecular data to support the hypothesis of Plachetzki *et al.* (2005) are limited to a few taxa (*e.g.*, the annelid *Platynereis*, the cubozoan *Tripedalia*, and the mouse). Sequence data from opsin and phototransduction signaling proteins expressed in molluscs will provide additional tests for this new view of photoreceptor evolution.

Conclusions

The range of molluscan eyes provides a diverse array of structures and functions and represent an excellent system for investigating developmental processes. In order to reap the rewards of this system, malacologists will need to take an interdisciplinary approach. Although tools developed and used in traditional model systems can be successfully applied to mollusc eyes, those interested in studying the molluscan eye must familiarize themselves with much of the existing eye literature and have an understanding of traditional model species used to study the eye. Therefore, these researchers must be trained in other biological fields with a diverse set of methods. In particular, advances in genomic techniques will make mollusc species more accessible to studying the genetics of the eye and its processes. Ultimately, these advances and new husbandry practices will allow the development of new molluscan species as models to study the eye.

It is important that molluscs are included in eye research, in part because molluscan eyes have much to offer developmental and cell biology, physiology, evolution, and ecology. The phylum provides a diversity of eye structures that possess a multitude of functions. Many times these highly diverse eyes are found within a species, providing opportunities to examine the genetic underpinnings of phenotypic variation. For cell biology, molluscan models have been successfully used to study cytoskeleton growth, which could provide clues that link its organization to retinal disease. In developmental biology, gene expression studies in molluscan models may offer insight in the mechanisms of cell differentiation and cell fate. Finally, the addition of molluscan taxa to the study of the eye will fill an evolutionary gap in understanding eye development and evolution.

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